(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 519 731 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
15.04.2009 Bulletin 2009/16

(21) Application number: **03738280.1**

(22) Date of filing: **13.06.2003**

(51) Int Cl.:
A61K 31/55 *(2006.01)* ***A61K 31/56*** *(2006.01)*
A61K 31/57 *(2006.01)* ***A61K 31/58*** *(2006.01)*
A61K 9/00 *(2006.01)* ***A61P 37/08*** *(2006.01)*
A61P 27/14 *(2006.01)* ***A61P 11/06*** *(2006.01)*

(86) International application number:
PCT/GB2003/002557

(87) International publication number:
WO 2003/105856 (24.12.2003 Gazette 2003/52)

(54) COMBINATION OF AZELASTINE AND FLUTICASONE

KOMBINATION VON AZELASTINE UND FLUTICASONE

ASSOCIATION D'AZELASTINE ET DE FLUTICASONE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR
Designated Extension States:
LT LV MK

(30) Priority: **14.06.2002 GB 0213739**

(43) Date of publication of application:
06.04.2005 Bulletin 2005/14

(73) Proprietor: **Cipla Ltd.**
Mumbai 400 008 (IN)

(72) Inventors:
- **LULLA, Amar**
  Mumbai 400 005 (IN)
- **MALHOTRA, Geena**
  Mumbai 400 010 (IN)

(74) Representative: **Curtis, Philip Anthony et al**
A.A. Thornton & Co.
235 High Holborn
London WC1V 7LE (GB)

(56) References cited:
EP-A- 0 780 127 **WO-A-97/01337**

- **DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 2000 PORTMANN D ET AL: "[Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine)]" Database accession no. NLM11233712 XP002252974 & REVUE DE LARYNGOLOGIE - OTOLOGIE - RHINOLOGIE. FRANCE 2000, vol. 121, no. 4, 2000, pages 273-279, ISSN: 0035-1334**
- **BUSSE W W ET AL: "CORTICOSTEROID-SPARING EFFECT OF AZELASTINE IN THE MANAGEMENT OF BRONCHIAL ASTHMA" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, AMERICAN LUNG ASSOCIATION, NEW YORK, NY, US, vol. 153, no. 1, 1996, pages 122-127, XP000604179 ISSN: 1073-449X**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 519 731 B1

Description

[0001] The present invention relates to pharmaceutical products according to claim 20 and formulations according to claim 1. More particularly the present invention relates to said pharmaceutical products and formulations useful for preventing or minimising allergic reactions. More particularly, but not exclusively, the present invention relates to said pharmaceutical products and formulations for nasal and ocular use.

[0002] Such allergic reactions commonly comprise the allergy-related and vasomotor-related symptoms and the rhinovirus-related symptoms.

[0003] It is known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions. Thus, for example, it is known to use the antihistamine azelastine (usually as the hydrochloride salt) as a nasal spray against seasonal or perennial allergic rhinitis, or as eye drops against seasonal and perennial allergic conjunctivitis.

[0004] It is also known to treat these conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions. Among the corticosteroids known for nasal use are, for example, beclomethasone, mometasone, fluticasone, budesonide and cyclosenide. Corticosteroids known for ocular anti-inflammatory use include betamethasone sodium, dexamethasone sodium and prednisolone acetate, for example.

[0005] It would be highly desirable, however, to provide a treatment that combines the effects of anti-histamine treatments and steroid treatments, in a pharmaceutically acceptable formulation, which is tolerated in situ, without significantly disrupting the potency of the constituent pharmaceuticals.

[0006] We have now found that, very surprisingly, azelastine (4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably in salt form and even more preferably in the form of the hydrochloride salt, can advantageously be combined with the steroid fluticasone, or a pharmaceutically acceptable ester thereof, to provide a stable, very effective combination product or formulation preferably for nasal or ocular treatment The combination can provide, in a single administration or dosing regime, the antihistaminic properties of azelastine and the anti-inflammatory (and/or other) properties of the steroid fluticasone, without any significant interference between the two, or adverse reaction in situ.

[0007] In one aspect the invention provides a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and fluticasone or a pharmaceutically acceptable ester thereof.

[0008] The term "physiologically functional derivative" as used herein denotes a chemical derivative of any of the specific therapeutic agents described herein having the same or similar physiological function as the free base therapeutic agent and, for example, being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

[0009] The preferred forms of formulations of the invention are nasal drops, eye drops, nasal sprays, nasal inhalation solutions or aerosols or insufflation powders.

[0010] Preferred embodiments of the invention can comprise stable aqueous solutions of azelastine or one or more of its salts, in combination with Fluticasone, which can be used in the form of inhalation solution, pressurized aerosol, eye drops or nasal drops, and in a particular preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can, for example, be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. In a preferred embodiment, 0.03 to 3 mg of azelastine base and 0.05 to 0.15 mg of fluticasone or ester thereof should be released per individual actuation.

[0011] The formulations preferably contain a preservative and/or stabilizer. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and its alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl phydroxybenzoates, chlorhexidine (for example in the form of the acetate or gluconate) and phenyl mercury borate. Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide" benzyldirnethyl-[2-[2-[p-(1,1,3,3-tetramethyl-butyl)phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05%, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride".

[0012] The total amount of preservatives in the formulations (solutions, ointments, etc.) is preferably from 0.001 to 0. 10g, preferably 0.01g per 100ml of solution/suspension or 100g of formulation.

[0013] In the case of preservatives, the following amounts of individual substances can, for example, be used: thimero sal 0.002-0.02%; benzalkonium chloride 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;); chlorhexidine acetate or gluconate 0.01 to 0.02%; phenyl mercuric/nitrate, borate, acetate 0.002-0.004%; p-hydroxybenzoic acid ester (for example, a mixture of the methyl ester and propyl ester in the ratio 7:3): preferably 0.05-0.15, more preferably 0.1 %.

[0014] The preservative used is preferably a combination of edetic acid (for example, as the disodium salt) and

benzalkonium chloride. In this combination, the edetic acid is preferably used in a concentration of 0.05 to 0.1%, benzalkonium chloride preferably being used in a concentration of 0.005 to 0.05%, more preferably 0.01%.

[0015] In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.

[0016] Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides and polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerisation of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine component

[0017] It is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol and NaCl.

[0018] The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50 to 0.56 degree C is attained in comparison to pure water.

[0019] In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example: Glucose $1H_2O$ 3.81g; saccharose 6.35g; glycerine 2.2g; 1,2-propylene glycol 1.617g; sorbitol 3.84g (in the case of mixtures of these substances correspondingly less may optionally be used).

[0020] Moreover, it is possible to add thickening agents to solutions according to the present invention to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.

[0021] Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

[0022] In the event of the use of hydroxypropyl cellulose, 0.1% by weight of the formulation, for example, is used for this purpose.

[0023] In the event of the use of Avicel RC 591 or CL11, 0.65-3.0% by weight of the formulation, for example, is used for the purpose.

[0024] It is also possible to add to the formulations buffer substances such as citric acid/sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), trometamol or equivalent conventional buffers in order, for example, to adjust the formulations to a pH value of 3 to 7, preferably 4.5 to 6.5.

[0025] The amount of citric acid is, for example, 0.01 to 0.14g, preferably 0.04 to 0.05g, the amount of disodium hydrogenphosphate 0.1 to 0.5g, preferably 0.2 to 0.3g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

[0026] In the case of solutions and suspensions, the maximum total concentration of active agent and buffer is preferably less than 5%, in particular less than 2% (weight/volume).

[0027] For the nasal application, a solution or suspension can preferably be used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

[0028] Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in combination with steroid, in the form of a solution or suspension in a so-called propellant The propellant may be a pressurized liquid chlorinated, fluorinated hydrocarbon or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutene or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. Hydrofluorocarbons (HFCs), such as HFC 134a, and HFC 227a can also be used, and are preferred for environmental reasons. The pressure packing has a dosage or metering valve which, on actuation, releases a defined amount of the solution or suspension of the medicament The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed in the nose or which are available for inspiration into the nose. Certain plastic applicators may be used to actuate the valve and to convey the sprayed suspension into the nose.

[0029] In the case of application as an aerosol, it is also possible to use a conventional adapter.

[0030] Particularly preferred embodiments of the present invention are hereinafter described and it will of course be appreciated that any of the previous description of suitable ingredients and formulation characteristics can also be applicable to the following products and formulations as provided by the present invention.

[0031] It will be appreciated, therefore, that the present invention further provides a pharmaceutical product comprising

(i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) the steroid fluticasone, or a pharmaceutically acceptable ester thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

[0032] It will also be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different pharmaceutical formulations, or separately or sequentially. If there is separate or sequential administration, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

[0033] Suitable propellants for use in pharmaceutical products of formulations as provided by the present invention include 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3,-heptafluoropropane (HFA 227), or a combination of both, or mono-fluoro trichloromethane and dichloro difluoromethane, in particular 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), with HFA 134a being preferred.

[0034] A pharmaceutical aerosol formulation according to the present invention preferably further comprises a polar cosolvent such as C_{2-6} aliphatic alcohols and polyols, for example ethanol, isopropanol and propylene glycol, with ethanol often being preferred. Preferably, the concentration of the cosolvent is in the range of about 2 to 10% by weight, typically up to about 5%, of the total formulation.

[0035] A pharmaceutical aerosol formulation according to the present invention may further comprise one or more surfactants. Such surfactants can be included to stabilise the formulations and for lubrication of a valve system. Some of the most commonly used surfactants in aerosol formulations are oils derived from natural sources, such as corn oil, olive oil, cottonseed oil and sunflower seed oil, and also phospholipids. Suitable surfactants can include lecithin, oleic acid or sorbitan oleate.

[0036] A further preferred embodiment of the present invention can be where a formulation or product is provided in the form of insufflatable powder, where preferably the maximum particle size of the substance suitably does not exceed 10μm. Azelastine or its salts and the fluticasone or its esters may be mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate, etc.

[0037] In one embodiment, the therapeutic agents employed have a particle size of less than about 10 μm, preferably less than 5 μm.

[0038] It will be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different insufflation powder formulations, or separately or sequentially. If there is separate or sequential administration as discussed above, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

[0039] Dry insufflation powder formulations as provided by the present invention can be beneficial where it is required that therapeutic agents as employed according to the present invention are retained in the nasal cavity, and systemic side effects can be minimised or eliminated. Furthermore, insufflation powder formulations as employed in the present invention can be beneficial whereby retention of azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, at the nasal mucosa is improved, and the bitter aftertaste associated with liquid antihistamine formulations significantly reduced, whilst also exhibiting the synergistic therapeutic effect associated with the azelastine/fluticasone combinations provided by the present invention. By providing a dry insufflation powder formulation of azelastine, together with fluticasone, having an average particle size of less than about 10 μm, the therapeutic agents can be restricted primarily to the desired target organ, the nasal mucosa.

[0040] A dry powder insufflation formulation according to the present invention can be administered by the use of an insufflator, which can produce a finely divided cloud of the dry powder. The insufflator preferably is provided with means to ensure administration of a substantially pre-determined amount of a formulation or product as provided by the present invention. The powder may be used directly with an insufflator which is provided with a bottle or container for the powder, or the powder may be filled into a capsule or cartridge, such as a gelatin capsule, or other single dose device adapted for administration. The insufflator preferably has means to open the capsule or other dose device.

[0041] Preferred combinations of therapeutic agents employed in pharmaceutical products and formulations according to the present invention (in particular nasal sprays or drops, aerosol or insufflation products and formulations as described above) comprise any one of the following combinations.

[0042] Thus, in another aspect of the present invention, there is provided a pharmaceutical product comprising (i)

azelastine, or a pharmaceutically acceptable salt thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated. Suitably the esters can be selected from fluticasone propionate and fluticasone valerate.

[0043] Specific combinations of therapeutic agents employed in pharmaceutical products and formulations according to the present invention comprise any one of the following combinations:

azelastine hydrochloride and fluticasone propionate; and
azelastine hydrochloride and fluticasone valerate.

[0044] The pharmaceutical products herein described may be used in methods for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, the methods comprising administrating a therapeutically effective amount of a pharmaceutical product substantially as hereinbefore described, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

[0045] The pharmaceutical formulations of the present invention may also be used in a method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, the methods comprising administrating a therapeutically effective amount of a pharmaceutical formulation substantially as hereinbefore described.

[0046] In another aspect of the present invention, there is provided the use, in the manufacture of a medicament for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, of a pharmaceutical product, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

[0047] The pharmaceutical products substantially as hereinbefore described, may be prepared by a process which comprises providing as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated: (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone, or a pharmaceutically acceptable ester thereof.

[0048] The pharmaceutical formulations substantially as hereinbefore described, may be prepared by a process which comprises admixing a pharmaceutically acceptable carrier or excipient with: (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and (ii) fluticasone or a pharmaceutically acceptable ester thereof Preferably pharmaceutical formulations according to the present invention can comprise insufflation powder formulations, nasal sprays, nasal inhalation solutions or aerosols substantially as hereinbefore described.

[0049] The present invention is now illustrated by the following Examples, which do not limit the scope of the invention in any way. Examples 2, 6, 7 and 8 are comparative examples. In Examples where only the ingredients of formulations according to the present invention are listed, these formulations are prepared by techniques well known in the art.

Example 1

[0050] Nasal spray or nasal drops with 0.1% azelastine hydrochloride as active ingredient and steroid 0.1%

Sr. No	Ingredients	Quantity %w/v
1.	Azelastine hydrochloride	0.1%
2.	Steroid	0.1%
3.	Disodium edetate	0.005%
4.	Sodium chloride	0.9%
5.	Benzalkonium chloride	0.001%
6.	Avicel RC 591	1.2%
7.	Citric acid monohydrate	0.2%
8.	Disodium hydrogen phosphate dodecahydrate	0.1%
9.	Purified water	

Example 2

[0051] Dosage aerosol giving off 0.5 mg of azelastine hydrochloride and 50 micrograms of beclomethasone dipropionate freon solvate per stroke.

[0052] About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dicblorotetufluoroethane are cooled to about -55 degree C in an appropriate cooling vessel. A mixture of 0.086 kg of pre-cooled sorbitantrioleate and 0.8600 kg of pre-cooled trichlorofluoromethane are dissolved with stirring into the mixture at -55 degrees C, 0.0688 kg of micronized azelastine hydrochloride, 0.00688 kg of beclomethasone dipropionate freon solvate and 0.0688 kg of micronized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about -55 degree C.

[0053] Following closure of the cooling vessel the suspension is again cooled to about -55 degrees C under intensive stirring. It is then ready to be filled.

Example 3

[0054]

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Fluticasone propionate	0.0357
	Glycerin	2.60
	Avicel RC 591	1.35
	Polysorbate 80	0.025
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.
*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg).		

Example 4

[0055]

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Fluticasone valerate	0.0357
	Glycerin	2.60
	Avicel RC 591	1.20
	Polysorbate 80	0.030
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25

(continued)

Sr. No.	Ingredients	Quantity (% w/w)
	Purified water	q. s.
*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone valerate (50 mcg).		

Example 5

[0056]

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Fluticasone propionate	0.0714
	Glycerin	2.60
	Avicel RC 581	1.35
	Polysorbate 80	0.025
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.
*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg).		

Example 6

[0057]

Nasal spray or nasal drops with Azelastine and steroid

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Mometasone Furoate	0.05173
	Glycerin	2.30
	Disodium edetate	0.005
	Polysorbate 80	0.0125
	Avicel RC 581	1.35
	Benzalkonium chloride	0.01
	Citric acid monohydrate	0.20
	Disodium hydrogen phosphate	0.10
	dodecahydrate	
	Purified water	q. s.

Example 7

[0058]

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Mometasone Furoate monohydrate	0.05173
	Glycerin	2.60
	Avicel CL 611	2.295
	Polysorbate 80	0.0125
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.
*Each spray delivers Azelastine Hydrochloride (140 mcg) and Mometasone furoate (50 mcg).		

Examples 8

[0059]

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Mometasone Furoate monohydrate	50
	HFA 134a	q.s.
	Lecithin	0.1%
	Alcohol	(up to 5%)

Example 9

[0060]

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone propionate	50
	HFA 134a	q.s.
	Sorbitan trioleate	0.1%
	Alcohol	(up to 5%)

Example 10

[0061]

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140

(continued)

Sr. No.	Ingredients	Quantity in mcg
	Fluticasone propionate	100
	HFA 134a	q.s.
	Oleic acid	0.1%

Example 11

[0062]

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone Valerate	50
	HFA 134a	q.s.
	Alcohol	(up to 5%)

[0063] Insufflatable powders containing Azelastine and Steroid:

Example 12

[0064]

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	50 mcg
	Lactose	q.s. (up to 25 mcg)

Example 13

[0065]

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	100 mcg
	Mannitol	q.s. (up to 30 mcg)

Example 14

[0066]

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	250 mcg
	Lactose	q.s. (up to 30 mcg)

Claims

1. A pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivatives thereof, and fluticasone or a pharmaceutically acceptable ester thereof.

2. A pharmaceutical formulation according to claim 1, wherein said azelastine is present as azelastine hydrochloride.

3. A formulation according to claim 1 or 2, wherein the steroid is fluticasone propionate or fluticasone valerate,

4. A formulation according to any of claims 1 to 3, which contains fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation.

5. A formulation according to any of claims 1 to 4, wherein the formulation has a particle size of less than about 10 μm, preferably less than 5 μm.

6. A formulation according to any of claims 1 to 5, which is a suspension containing 0.0005 to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the formulation) of fluticasone or a pharmaceutically acceptable ester thereof.

7. A formulation according to claim 6, which contains from 0.001 to 1 % (weight/weight of the formulation) azelastine, or salt thereof, and from 0.5% to 1.5% (weight/weight of the formulation) fluticasone or a pharmaceutically acceptable ester thereof.

8. A formulation according to any of claims 1 to 7, which also contains a surfactant, comprising a polysorbate or poloxamer surfactant.

9. A formulation according to claim 8, which contains from about 50 micrograms to about 1 milligram, of surfactant per ml of the formulation.

10. A formulation according to any of claims 1 to 9, which also contains an isotonic agent comprising sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

11. A formulation according to any of claims 1 to 10, which also contains at least one of a buffer, a preservative and a suspending or thickening agent, wherein said preservative is selected from edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine, phenyl mercury borate, or benzoic acid or a salt, a quaternary ammonium compound, or sorbic acid or a salt thereof, the suspending agent or thickening agent is selected from cellulose derivatives, gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, or pectin, and the buffer comprises a citric acid-citrate buffer.

12. A formulation according to any of claims 11, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7, preferably 4.5 to about 6.5.

13. A formulation according to any preceding claim, which comprises azelastine hydrochloride and fluticasone propionate.

14. A formulation according to any preceding claim, which comprises azelastine hydrochloride and and fluticasone valerate.

15. A formulation according to any of claims 1 to 14, which is in the form of an insufflation powder.

16. A formulation according to any of claims 1 to 15, which is an aqueous suspension or solution.

17. A formulation according to claim 16, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray or an inhalation solution.

18. A formulation according to claim 17, which is in the form of nasal drops or nasal spray.

19. A formulation according to claim 17, which is in the form of an aerosol.

20. A pharmaceutical product comprising (i) azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, as a combined preparation for use in medecine, said (i) azelastine and (ii) fluticasone being in the form of an aerosol formulation for MDI delivery, in the form of an insufflation powder, or in the form of a nasal spray.

21. A pharmaceutical product according to claim 20, which comprises azelastine hydrochloride and fluticasone propionate.

22. A pharmaceutical product according to claim 20, which comprises azelastine hydrochloride and and fluticasone valerate.

23. A pharmaceutical product according to claim 20, 21 or 22, for use as a nasal spray in the treatment of seasonal allergic rhinitis, perennial allergic rhinitis.

24. A, pharmaceutical product according to claim 20, 21 or 22, for use as eye drops in the treatment of seasonal allergic conjunctivitis, perennial allergic conjunctivitis.

Patentansprüche

1. Pharmazeutische Formulierung, die Azelastin oder ein pharmazeutisch unbedenkliches Salz, Solvat oder physiologisch funktionales Derivat davon und Fluticason oder einen pharmazeutisch unbedenklichen Ester davon umfasst.

2. Pharmazeutische Formulierung nach Anspruch 1, wobei das Azelastin als Azelastinhydrochlorid vorliegt.

3. Formulierung nach Anspruch 1 oder 2, wobei es sich bei dem Steroid um Fluticasonpropionat oder Fluticasonvalerat handelt.

4. Formulierung nach einem der Ansprüche 1 bis 3, die Fluticason oder einen pharmazeutisch unbedenklichen Ester davon in einer Menge von etwa 50 Mikrogramm/ml bis etwa 5 mg/ml der Formulierung enthält.

5. Formulierung nach einem der Ansprüche 1 bis 4, wobei die Formulierung eine Teilchengröße von weniger als etwa 10 μm, vorzugsweise weniger als 5 μm aufweist.

6. Formulierung nach einem der Ansprüche 1 bis 5, bei der es sich um eine Suspension handelt, die 0,0005 bis 2 % (Gew.-% der Formulierung) Azelastin oder eines pharmazeutisch unbedenklichen Salzes von Azelastin und von 0,5 bis 1,5 % (Gew.-% der Formulierung) Fluticason oder eines pharmazeutisch unbedenklichen Esters davon enthält.

7. Formulierung nach Anspruch 6, die von 0,001 bis 1 % (Gew.-% der Formulierung) Azelastin oder eines Salzes davon und von 0,5 % bis 1,5 % (Gew.-% der Formulierung) Fluticason oder eines pharmazeutisch unbedenklichen Esters davon enthält.

8. Formulierung nach einem der Ansprüche 1 bis 7, die außerdem ein Tensid enthält, das ein Polysorbat- oder Poloxamer-Tensid umfasst.

9. Formulierung nach Anspruch 8, die von etwa 50 Mikrogramm bis etwa 1 Milligramm Tensid pro ml der Formulierung enthält.

10. Formulierung nach einem der Ansprüche 1 bis 9, die außerdem ein isotones Mittel enthält, das Natriumchlorid, Saccharose, Glucose, Glycerin, Sorbit oder 1,2-Propylenglykol umfasst.

11. Formulierung nach einem der Ansprüche 1 bis 10, die außerdem einen Puffer, ein Konservierungsmittel und/oder ein Suspendier- oder Verdickungsmittel enthält, wobei das Konservierungsmittel aus Edetinsäure und deren Alkalisalzen, Niederalkyl-p-hydroxybenzoaten, Chlorhexidin, Phenylquecksilberborat oder Benzoesäure oder einem Salz, einer quartären Ammoniumverbindung oder Sorbinsäure oder einem Salz davon ausgewählt ist, das Suspen-

dier- oder Verdikkungsmittel aus Cellulosederivaten, Gelatine, Polyvinylpyrrolidon, Tragant, Ethoxose (wasserlösliche Binde- und Verdickungsmittel auf der Basis von Ethylcellulose), Alginsäure, Polyvinylalkohol, Polyacrylsäure oder Pektin ausgewählt ist und der Puffer einen Citronensäure-/Citratpuffer umfasst.

12. Formulierung nach Anspruch 11, wobei der Puffer den pH-Wert der wässrigen Phase auf 3 bis 7, vorzugsweise 4,5 bis etwa 6,5 hält.

13. Formulierung nach einem der vorhergehenden Ansprüche, die Azelastinhydrochlorid und Fluticasonpropionat umfasst.

14. Formulierung nach einem der vorhergehenden Ansprüche, die Azelastinhydrochlorid und Fluticasonvalerat umfasst.

15. Formulierung nach einem der Ansprüche 1 bis 14, die in der Form eines Insufflationspulvers ist.

16. Formulierung nach einem der Ansprüche 1 bis 15, bei der es sich um eine wässrige Suspension oder Lösung handelt.

17. Formulierung nach Anspruch 16, die in der Form eines Aerosols, einer Salbe, von Augentropfen, von Nasentropfen, eines Nasensprays oder einer Inhalationslösung ist.

18. Formulierung nach Anspruch 17, die in der Form von Nasentropfen oder eines Nasensprays ist.

19. Formulierung nach Anspruch 17, die in der Form eines Aerosols ist.

20. Pharmazeutisches Produkt, das (i) Azelastin oder ein pharmazeutisch unbedenkliches Salz, Solvat oder physiologisch funktionales Derivat davon und (ii) Fluticason oder einen pharmazeutisch unbedenklichen Ester davon als ein Kombinationspräparat zur Verwendung in der Medizin umfasst, wobei das (i) Azelastin und das (ii) Fluticason in der Form einer Aerosolformulierung zur Abgabe mittels Dosierinhalator, in der Form eines Insufflationspulvers oder in der Form eines Nasensprays sind.

21. Pharmazeutisches Produkt nach Anspruch 20, das Azelastinhydrochlorid und Fluticasonpropionat umfasst.

22. Pharmazeutisches Produkt nach Anspruch 20, die Azelastinhydrochlorid und Fluticasonvalerat umfasst.

23. Pharmazeutisches Produkt nach Anspruch 20, 21 oder 22 zur Verwendung als ein Nasenspray bei der Behandlung von allergischer saisongebundener Rhinitis, perennialer allergischer Rhinitis.

24. Pharmazeutisches Produkt nach Anspruch 20, 21 oder 22 zur Verwendung als Augentropfen bei der Behandlung von allergischer saisongebundener Rhinitis, perennialer allergischer Rhinitis.

Revendications

1. Formulation pharmaceutique qui comprend de l'azélastine, ou un sel, solvate ou dérivé physiologiquement fonctionnel pharmaceutiquement acceptable de celle-ci, et de la fluticasone ou un ester pharmaceutiquement acceptable de celle-ci.

2. Formulation pharmaceutique selon la revendication 1, dans laquelle ladite azélastine est présente comme chlorhydrate d'azélastine.

3. Formulation selon la revendication 1 ou la revendication 2, dans laquelle le stéroïde est du propionate de fluticasone ou du valérate de fluticasone.

4. Formulation selon l'une quelconque des revendications 1 à 3, qui contient du fluticasone ou un ester pharmaceutiquement acceptable de celle-ci dans une quantité allant d'environ 50 microgrammes / ml à environ 5 mg / ml de la formulation.

5. Formulation selon l'une quelconque des revendications 1 à 4, dans laquelle la formulation présente une taille de particules inférieure à environ 10 μm, de préférence inférieure à 5 μm.

6. Formulation selon l'une quelconque des revendications 1 à 5, qui est une suspension contenant 0,0005 à 2 % (poids / poids de la formulation) d'azélastine ou d'un sel d'azélastine pharmaceutiquement acceptable, et de 0,5 à 1,5 % (poids / poids de la formulation) de fluticasone ou d'un ester pharmaceutiquement acceptable de celle-ci.

7. Formulation selon la revendication 6, qui contient de 0,001 à 1 % (poids / poids de la formulation) d'azélastine, ou un sel de celle-ci, et de 0,5 % à 1,5 % (poids / poids de la formulation) de fluticasone ou d'un ester pharmaceutiquement acceptable de celle-ci.

8. Formulation selon l'une quelconque des revendications 1 à 7, qui contient également un tensioactif, comprenant un polysorbate ou un tensioactif poloxamère.

9. Formulation selon la revendication 8, qui contient d'environ 50 microgrammes à environ 1 milligramme de tensioactif par ml de la formulation.

10. Formulation selon l'une quelconque des revendications 1 à 9, qui contient également un agent isotonique comprenant du chlorure de sodium, du saccharose, du glucose, de la glycérine, du sorbitol ou du 1,2-propylèneglycol.

11. Formulation selon l'une quelconque des revendications 1 à 10, qui contient également au moins un parmi un tampon, un conservateur et un agent dispersant ou épaississant, dans laquelle ledit conservateur est sélectionné parmi de l'acide édétique et ses sels alcalins, des p-hydroxybenzoates d'alkyle inférieur, de la chlorhexidine, du borate de phényle mercure, ou de l'acide benzoïque ou un sel, un composé ammonium quaternaire, ou de l'acide sorbique ou un sel de celui-ci, l'agent dispersant ou l'agent épaississant est sélectionné parmi des dérivés de cellulose, de la gélatine, de la polyvinylpyrrolidone, de la gomme adragante, de l'ethoxose (agents agglutinant et épaississant solubles dans l'eau sur la base d'éthylcellulose), de l'acide alginique, de l'alcool polyvinylique, de l'acide polyacrylique, ou de la pectine, et le tampon comprend un tampon acide citrique - citrate.

12. Formulation selon l'une quelconque des revendications 11, dans laquelle le tampon conserve le pH de la phase aqueuse de 3 à 7, de préférence de 4,5 à environ 6,5.

13. Formulation selon l'une quelconque des revendications précédentes, qui comprend du chlorhydrate d'azélastine et du propionate de fluticasone.

14. Formulation selon l'une quelconque des revendications précédentes, qui comprend du chlorhydrate d'azélastine et du valérate de fluticasone.

15. Formulation selon l'une quelconque des revendications 1 à 14, qui est sous la forme d'une poudre d'insufflation.

16. Formulation selon l'une quelconque des revendications 1 à 15, qui est une suspension ou une solution aqueuse.

17. Formulation selon la revendication 16, qui est sous la forme d'un aérosol, un onguent, des gouttes oculaires, des gouttes nasales, un pulvérisateur nasal ou une solution d'inhalation.

18. Formulation selon la revendication 17, qui est sous la forme de gouttes nasales ou d'un pulvérisateur nasal.

19. Formulation selon la revendication 17, qui est sous la forme d'un aérosol.

20. Produit pharmaceutique comprenant (i) de l'azélastine, ou un sel, un solvate ou un dérivé physiologiquement fonctionnel pharmaceutiquement acceptable de celle-ci, et (ii) de la fluticasone ou un ester pharmaceutiquement acceptable de celle-ci, comme préparation combinée à utiliser en médecine, lesdites (i) azélastine et (ii) fluticasone étant sous la forme d'une formulation d'aérosol pour une diffusion par pompe, sous la forme d'une poudre d'insufflation, ou sous la forme d'un vaporisateur nasal.

21. Produit pharmaceutique selon la revendication 20, qui comprend du chlorhydrate d'azélastine et du propionate de fluticasone.

22. Produit pharmaceutique selon la revendication 20, qui comprend du chlorhydrate d'azélastine et du valérate de fluticasone.

23. Produit pharmaceutique selon la revendication 20, la revendication 21 ou la revendication 22, à utiliser comme vaporisateur nasal dans le traitement de la rhinite allergique saisonnière, et de la rhinite allergique apériodique.

24. Produit pharmaceutique selon la revendication 20, la revendication 21 ou la revendication 22, à utiliser comme gouttes oculaires dans le traitement de la conjonctivite allergique saisonnière, et de la conjonctivite allergique apériodique.